SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. General Information

Device Generic Name:	Intravascular Stent
Device Trade Name:	NIRflex™ Premounted Coronary Stent System
Applicant's Name and Address:	Medinol Ltd PO Box 58165 Kiryad Atidim Bldg. 3, Entrance 2, 5th Floor 61581 Tel Aviv, Israel
U.S. Representative:	Medinol, Ltd. 28 State Street Boston, MA 02109
Date of Panel Recommendation:	none
PMA Number:	P020040
Date of Notice of Approval to Applicant:	October 24, 2003

2. Indications for Use

The NIRflex™ Premounted Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* and restenotic lesions in native coronary arteries (length less than or equal to 25mm) with a reference vessel diameter from 2.5 mm to 4.0 mm.

Long-term outcome (beyond 6 months) for this permanent implant is unknown at present.

3. Contraindications

Do not use the NIRflex™ Premounted Coronary Stent System in:

- Patients in whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.
- Patients with known allergies to stainless steel.

4. Warnings and Precautions

Please refer to the device labeling for a list of warnings and precautions.

5. Device Description

The NIRflex™ Premounted Coronary Stent System is comprised of a balloon expandable stainless steel (316LS) NIRflex™ stent, pre-mounted on a HSC 135 rapid exchange (RE) delivery system. The NIRflex™ Premounted Coronary Stent System is available in nominal diameters of 2.5, 2.75, 3.0, 3.5 and 4.0 mm and lengths of 9, 12, 16, 20, 24, and 32 mm.

The NIRflex™ stent is mounted (machine crimped) on the distal end of a HSC 135 RE balloon catheter. The stent is mounted between two radiopaque gold markers that in conjunction with fluoroscopy aid in accurate placement of the premounted stent in the artery for stent deployment. The delivery system is compatible with 0.014-inch diameter guide wires. The NIRflex™ Premounted Coronary Stent System device specifications are listed in Table 1.

Table 1: NIRflex™ Premounted Coronary Stent System Device Specifications

Catalog #	Stent Diameter	Stent Length	Minimum I.D. of Guiding Catheter* (in./mm)	Nominal Pressure (atm)	Rated Burst Pressure (atm)
421250090001	2.5 mm	9 mm	0.065 / 1.65	9	16
421250120001		12 mm	0.065 / 1.65	9	16
421250160001		16 mm	0.065 / 1.65	9	16
421250200001		20 mm	0.065 / 1.65	9	16
422275090001	2.75 mm	9 mm	0.065 / 1.65	7	16
422275120001		12 mm	0.065 / 1.65	7	16
422275160001		16 mm	0.065 / 1.65	7	16
422275200001		20 mm	0.065 / 1.65	7	16
422275240001		24 mm	0.065 / 1.65	7	16
422275320001		32 mm	0.065 / 1.65	7	16
422300090001	3.0 mm	9 mm	0.065 / 1.65	7	16
422300120001		12 mm	0.065 / 1.65	7	16
422300160001		16 mm	0.065 / 1.65	7	16
422300200001		20 mm	0.065 / 1.65	7	16
422300240001		24 mm	0.065 / 1.65	7	16
422300320001		32 mm	0.065 / 1.65	7	16
422350090001	3.5 mm	9 mm	0.065 / 1.65	7	16
422350120001		12 mm	0.065 / 1.65	7	16

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Catalog #	Stent Diameter	Stent Length	Minimum I.D. of Guiding Catheter* (in./mm)	Nominal Pressure (atm)	Rated Burst Pressure (atm)
422350160001		16 mm	0.065 / 1.65	7	16
422350200001		20 mm	0.065 / 1.65	7	16
422350240001		24 mm	0.065 / 1.65	7	16
422350320001		32 mm	0.065 / 1.65	7	16
420400090001	4.0 mm	9 mm	0.065 / 1.65	7	14
420400120001		12 mm	0.065 / 1.65	7	14
420400160001		16 mm	0.065 / 1.65	7	14
420400200001		20 mm	0.065 / 1.65	7	14
420400240001		24 mm	0.065 / 1.65	7	14
420400320001		32 mm	0.065 / 1.65	7	14

* See individual manufacturer specifications for (F) equivalent

6. Alternative Practices or Procedures

Alternative treatments for patients with coronary artery disease are exercise, diet and drug therapy, Percutaneous Transluminal Coronary Angioplasty (PTCA), coronary artery bypass graft (CABG) surgery or stenting with commercially available stents.

7. Marketing History

The NIRflex™ Premounted Coronary Stent System is registered for sale in Canada, Israel and Poland. The NIRflex™ Premounted Coronary Stent System received CE Mark approval on March 13, 2002 and is being marketed in the European Community countries.

The NIRflex™ Premounted Coronary Stent System has not been withdrawn in any country due to reasons related to safety and effectiveness of the device.

8. Adverse Events

8.1. Observed Adverse Events

A total of 205 patients were enrolled in a multi-center clinical study, to collect information about the safety and effectiveness of the NIRflex™ Premounted Coronary Stent System in the treatment of stenotic lesions in native coronary arteries (NIRflex™ US Study). These results were compared to results of the 848 patients treated with the NIR® PRIMO Stent System and the JJIS Palmaz-Schatz® Stent in the NIRVANA

Randomized Clinical Trial (NIRVANA RCT). These patients form the basis of the observed events reported.

Table 2 shows the results of patients receiving NIRflex™ Premounted Coronary Stent System (NIRflex™ US Study) along with those receiving the NIR® Primo Stent system and the Palmaz-Schatz® Stent (NIRVANA Study) during 6 months.

Table 2: Adverse Events during 6 Months Follow-Up
All patients in NIRflex™ US Study and NIRVANA RCT
%, [95% Confidence Interval], (Number)

Event	NIRflex™ US (N=205 pts)	NIRVANA (N=848 pts)	Difference [95% C.I.]
MACE (Death, MI, TLR)	10.5% (21/205)	11.1% (94/848)	-0.8% [-5.5%, 3.8%]
Early (in-hospital)	2.9% (6/205)	4.1% (35/848)	-1.2% [-3.9%, 1.5%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%,0.1%]
Out-of-hospital (180-Days)	7.3% (15/205)	7.0% (59/848)	0.4% [-3.6%, 4.3%]
Death – Total	0.5% (1/205)	0.7% (6/848)	-0.2% [-1.3%, 0.9%]
Early (in-hospital)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%, 0.1%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.0% (0/848)	-0.0% [0.0%,0.0%]
Out-of-hospital (180-Days)	0.5% (1/205)	0.6% (5/848)	-0.1% [-1.2%, 1.0%]
MI – Total	3.9% (4/205)	4.2% (36/848)	-0.3% [-3.3%, 2.6%]
Early (in-hospital)	2.9% (6/205)	3.8% (32/848)	-0.8% [-3.5%, 1.8%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%,0.1%]
Out-of-hospital (180-Days)	1.0% (2/205)	0.5% (4/848)	0.5% [-0.9%, 1.9%]
Q-wave MI – Total	0.5% (1/205)	0.7% (6/848)	-0.2% [-1.3%, 0.9%]
Early (in-hospital)	0.0% (0/205)	0.7% (6/848)	-0.7% [-1.3%, -0.1%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%,0.0%]
Out-of-hospital (180-Days)	0.5% (1/205)	0.0% (0/848)	0.5% [-0.5%, 1.4%]
Non Q-wave MI – Total	3.4% (7/205)	3.5% (30/848)	-0.1% [-2.9%, 0.7%]
Early (in-hospital)	2.9% (6/205)	3.1% (26/848)	-0.1% [-2.7%, 2.4%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%,0.1%]
Out-of-hospital (180-Days)	0.5% (1/205)	0.5% (4/848)	0.0% [-1.0%, 1.1%]
Emergent CABG – Total	0.5% (1/205)	0.1% (1/848)	0.4% [-0.6%, 1.4%]
Early (in-hospital)	0.5% (1/205)	0.1% (1/848)	0.4% [-0.6%, 1.4%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%,0.0%]
Out-of-hospital (180-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%, 0.0%]
TLR – Total	6.3% (13/205)	7.3% (62/848)	-1.0% [-4.7%, 2.8%]
Early (in-hospital)	0.5% (1/205)	0.7% (6/848)	-0.2% [-1.3%, 0.9%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%,0.1%]
Out-of-hospital (180-Days)	5.9% (12/205)	6.6% (56/848)	-0.8% [-4.4%, 2.9%]
TL-CABG – Total	1.0% (2/205)	6.0% (51/848)	-5.0% [-7.1%, -2.9%]
Early (in-hospital)	0.5% (1/205)	0.5% (4/848)	0.0% [-1.0%, 1.1%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%,0.1%]
Out-of-hospital (180-Days)	0.5% (1/205)	5.5% (47/848)	-5.1% [-6.9%, -3.2%]

Event	NIRflex™ US (N=205 pts)	NIRVANA (N=848 pts)	Difference [95% C.I.]
TL-PTCA – Total	5.9% (12/205)	2.0% (17/848)	3.8% [0.5%, 7.2%]
Early (in-hospital)	0.5% (1/205)	0.2% (2/848)	0.3% [-0.8%, 1.3%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%,0.0%]
Out-of-hospital (180-Days)	5.4% (11/205)	1.8% (15/848)	3.6% [0.4%, 6.8%]
TVR not involving the Target Lesion – Total	2.0% (4/205)	2.0% (17/848)	-0.1% [-2.2%, 2.1%]
Early (in-hospital)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%, 0.1%]
Out-of-hospital (30-Days)	0.5% (1/205)	0.2% (2/848)	0.3% [-0.8%,1.3%]
Out-of-hospital (180-Days)	2.0% (4/205)	1.8% (15/848)	0.2% [-1.9%, 2.3%]
TV/non-TL-CABG – Total	0.5% (1/205)	1.9% (16/848)	-1.4% [-2.7%, -0.1%]
Early (in-hospital)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%, 0.1%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.2% (2/848)	-0.2% [-0.6%,0.1%]
Out-of-hospital (180-Days)	0.5% (1/205)	1.7% (14/848)	-1.2% [-2.4%, 0.1%]
TV/non-TL-PTCA – Total	1.5% (3/205)	0.1% (1/848)	1.3% [-0.3%, 3.0%]
Early (in-hospital)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%, 0.0%]
Out-of-hospital (30-Days)	0.5% (1/205)	0.0% (0/848)	0.5% [-0.5%,1.4%]
Out-of-hospital (180-Days)	1.5% (3/205)	0.1% (1/848)	1.3% [-0.3%, 3.0%]
Stent thrombosis – Total	0.5% (1/205)	0.5% (4/848)	0.0% [-1.0%, 1.1%]
Early (in-hospital)	0.5% (1/205)	0.4% (3/848)	0.1% [-0.9%, 1.2%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%,0.1%]
Out-of-hospital (180-Days)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%, 0.1%]
Perforation – Total	0.0% (0/205)	0.5% (4/848)	-0.5% [-0.9%, 0.0%]
Early (in-hospital)	0.0% (0/205)	0.5% (4/848)	-0.5% [-0.9%, 0.0%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%,0.0%]
Out-of-hospital (180-Days)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%, 0.0%]
Bleeding complications – Total	1.5% (3/205)	1.2% (10/848)	0.3% [-1.5%, 2.1%]
Early (in-hospital)	1.0% (2/205)	1.1% (9/848)	-0.1% [-1.6%, 1.4%]
Out-of-hospital (30-Days)	0.5% (1/205)	0.1% (1/848)	0.4% [-0.6%,1.4%]
Out-of-hospital (180-Days)	0.5% (1/205)	0.1% (1/848)	0.4% [-0.6%, 1.4%]
Vascular complications – Total	3.4% (7/205)	4.5% (38/848)	-1.1% [-3.9%, 1.8%]
Early (in-hospital)	2.9% (6/205)	3.9% (33/848)	-1.0% [-3.6%, 1.7%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.6% (5/848)	-0.6% [-1.1%,-0.1%]
Out-of-hospital (180-Days)	0.5% (1/205)	0.6% (5/848)	-0.1% [-1.2%, 1.0%]
CVA – Total	0.0% (0/205)	0.4% (3/848)	-0.4% [-0.8%, 0.0%]
Early (in-hospital)	0.0% (0/205)	0.0% (0/848)	0.0% [0.0%, 0.0%]
Out-of-hospital (30-Days)	0.0% (0/205)	0.1% (1/848)	-0.1% [-0.3%,0.1%]
Out-of-hospital (180-Days)	0.0% (0/205)	0.4% (3/848)	-0.4% [-0.8%, 0.0%]

More than one event may be reported for a given patient in this table

Adverse Events Definitions:

Major Adverse Cardiac Events (MACE): Death, myocardial infarction, and target lesion revascularization.

Death: *Cardiac Death* was defined as death due to any of the following: 1) Acute myocardial infarction; 2) Cardiac perforation/pericardial tamponade; 3) Arrhythmia or conduction abnormality; 4) Cerebrovascular accident within 30 days of the procedure or cerebrovascular accident suspected of being related to the procedure; 5) Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; 6) Death due to suspected cardiogenic shock or other causes of shock suspected of being related to the procedure; 7) Any death in which a cardiac cause cannot be fully excluded; *Non-cardiac death* was defined as death not due to cardiac causes (as defined above)

Myocardial Infarction (MI): Myocardial infarction was classified as follows: *Q wave MI*: development of new, pathological Q waves in 2 or more contiguous leads (as assessed by the ECG core laboratory) with post-procedure CK or CKMB levels elevated above normal; *Non-Q wave MI*: elevation of post-procedure CK levels to >2 times normal with CKMB elevated above normal in the absence of pathological Q waves; if no assay for CKMB was performed, elevation of CK levels to >2 times normal without new Q waves was also considered a non-Q wave MI.

Target Lesion Revascularization (TLR): Any "clinically driven" repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

CABG: Coronary Artery Bypass Graft surgery.

PTCA: Percutaneous Transluminal Coronary Angioplasty.

Stent thrombosis: Angiographic documentation of stent occlusion within 30 days of the index procedure; or, any death within 30 days of the index procedure that is not clearly related to causes other than stent occlusion.

Perforation: Perforations were classified as follows: *Angiographic perforation:* perforation detected by the clinical site or the core laboratory at any point during the procedure; *Clinical perforation:* perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death; *Pericardial hemorrhage/tamponade:* perforation causing tamponade.

Bleeding complications: Transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular complications: Vascular complication is defined as the occurrence of any of the following in relation to the index procedure: 1) Hematoma at access site >5 cm; 2) False aneurysm; 3) AV fistula; 4) Retroperitoneal bleed; 5) Peripheral ischemia/nerve injury; 6) Procedure related transfusion; 7) Vascular surgical repair; 8) Ultrasound guided therapy (e.g. compression thrombin injection).

CVA: Acute neurologic deficit that is consistent with focal cerebral ischemia and **persists >24 hours** or is associated with new area of "infarct" on cerebral imaging study.

8.2. Potential Adverse Events

Adverse events may be associated with the use of a coronary stent in native coronary arteries (including those listed in Table 2):

- Acute myocardial infarction
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to anti-platelet agents/contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent Coronary Artery Bypass Surgery
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection and pain at insertion site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident
- Total occlusion of coronary artery

9. Summary of Pre-Clinical Studies

9.1. Biocompatibility Testing

The NIRFLEX™ stent utilizes a 316LS Stainless Steel (SS) that meets standard ASTM F 139. The stent is manufactured using the identical processes to those of the commercially available NIR® Stent. Therefore, biocompatibility testing previously completed on sterilized NIR® Stent was used to support the NIRFLEX™ stent.

All testing was conducted according to International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing," was submitted in the PMA, and consisted of the following:

- Cytotoxicity
- Systemic Injection Study, Sodium chloride and Cottonseed Extracts
- Intracutaneous Toxicity, Sodium chloride and Cottonseed Extracts
- Hemolysis - Rabbit Blood
- Salmonella Mutagenicity Test

- Ames Mutagenicity Assay
- Kligman Maximization Study
- Intramuscular Implantation Test – Subchronic, 30 day
- Pyrogen, LAL Test
- Lee and White Coagulation Test (hemocompatibility)
- Heavy Metals

All test results demonstrated that the stent was biocompatible and acceptable for its intended use.

Biocompatibility testing of the HSC 135 delivery system was conducted separately per International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing" and consisted of the following:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Hemolysis
- Coagulation

The above test results demonstrated that the stent delivery system materials are considered biocompatible and acceptable for their intended use.

9.2. *In Vivo* Animal Testing

The NIRFLEX™ stent was evaluated in two separate animal studies at the animal facility of Brigham & Women's Hospital, an Affiliate of the Harvard Medical School, Boston, MA. Both studies were conducted using experimental protocols that conform to GLP regulations.

The first study was designed to evaluate the potential impact of arterial curvature and stent length on the vascular response to stent implantation. The NIRFLEX™ stents were provided bare (un-mounted) and the balloon delivery catheter was the MAXXUM balloon. 32 mm stents were implanted in curved segments of porcine coronary arteries, and the arteries were harvested 28 days after implantation. The 28-day morphometric analysis showed expected results in terms of neointimal thickening and injury scores along the stent length. The overall performance of the NIRflex™ was acceptable, raising no safety concerns.

In the second animal study, the restenosis rate, characterization of the stent material, and its biological effect in a porcine vascular model were evaluated. For this study, short (9 mm) NIRflex™ stents were premounted on HSC 135 balloon catheters using a hand-crimping machine. The arteries were harvested at 28 days. The study demonstrated tissue responses consistent with stenting at 28 days after porcine coronary stent implantation.

Quantitative angiographic and histomorphometric analyses confirmed that there were no toxicity concerns over the full range of assessment parameters in aggregate and for sections taken at the proximal, middle and distal portion of the stents.

9.3. *In Vitro* Bench Testing

The *in vitro* bench testing was divided into two categories: the NIRflex™ Material Specification Conformance Testing and the NIRflex™ Stent Integrity Testing. All testing were performed per FDA's "Guidance for the Submission of Research and Marketing Application for Interventional Cardiology Devices: PTCA Catheters, Atherectomy Catheters, Lasers, Intravascular Stents, May 1995" and in accordance with Medinol Ltd. Design Verification Master Plan. The following tests were performed on the NIRflex™ Stent:

Test Method	Acceptance Criteria	Results Pass/Fail
Stent Raw Material Specification Conformance Testing: • Material Analysis • Mechanical Properties	ASTM-F139 Tensile Strength = 485 MPa (minimum) Elongation ≥ 40%	Tensile Strength = 293 MPa Elongation = 48.75% PASS
Corrosion test (3 groups of 9; n=27)	ASTM-G 61 > 500 mV	All groups had means that were > 1000 mV PASS
Metal to Artery Ratio (n=3 for each stent diameter)	2.5 mm stent ≤ 25% 2.75 – 4 mm ≤ 20%	Values range 9.6 – 17.6% PASS
Stent Foreshortening (n=3 for each stent grouping, length/diameter)	Foreshortening ≤ 20%	 PASS
Stent Expansion Uniformity (SEU) (groupings total, n=30)	SEU ≤ 5%	 PASS
Stent Conformability (2mm Deflection Force) n=6 each – Nirflex n=3 each – NIR®	2x control (NIR® stent) value	2.5, 3.5, and 5 mm stents (6.7, 10.5, 19.3) Nirflex (62.2, 71.2, 105.1) NIR® PASS
Compression test	2.5 mm "similar" or > NIR® 2.75 – 4.0 mm ≥ NIR®	Nirflex™ NIR 2.5 12.58 13.60 3.5 13.57 10.30 4.0 9.76 7.50 5.0 8.50 6.70 PASS

<table>
<tr><td>Accelerated Fatigue test:
• Bend & Rotate Test

• Ten years accelerated Test Inflation/Deflation pressure 50-150 mm Hg; Frequency 50 Hz</td><td>Cycles to failure ≥ NIR®

Free of strut failure
Free of corrosion
Breakdown potential > 500 mV</td><td>Nirflex™ 6 & 8 cell stents
NIR® 7 & 9 cell stents

Nirflex™ NIR®
15500 3000
23000 22500
(Range of cycles)

Visually free of failure or corrosion; 1059.8 mV

PASS</td></tr>
<tr><td>Recoil Test (n=27)</td><td>Stent Recoil < 5%</td><td>Recoil range 1.8% – 2.9%</td></tr>
<tr><td>Finite Element Analysis of Stent Expansion and Over Expansion</td><td>No stent failure (40% strain) under modeling conditions</td><td>Modeling and experimental data demonstrated that the stent did not fail during expansion/over-expansion

PASS</td></tr>
<tr><td>Goodman Analysis</td><td>-NA-</td><td>Finite Element Analysis (FEA) was used to analyze stent fatigue.</td></tr>
<tr><td>Stent Over Expansion and Safety Margin (n=135)</td><td>No stent breakage when the stent meets the following criteria:

<table><tr><td>Stent dia</td><td>Over-expansion dia.</td></tr><tr><td>2.5</td><td>3.25</td></tr><tr><td>2.75-3.5</td><td>4.25</td></tr><tr><td>4.0</td><td>5.75</td></tr></table></td><td>No failures

PASS</td></tr>
<tr><td>Weld Quality (n=92)</td><td>No detected weld defects</td><td>PASS</td></tr>
<tr><td>Dimensional Verification</td><td>• All samples comply with strut width
• Electorpolishing of each lot maintained
• Stent weight meets specifications
• All devices microscopically inspected for flaws
• All devices inspected for “mix-ups”</td><td>

PASS</td></tr>
</table>

The following tests were performed to evaluate performance characteristics and safety of the NIRflex™ Premounted Coronary Stent System delivery system:

<table>
<tr><th>Test Method</th><th>Acceptance Criteria</th><th>Results
Pass/Fail</th></tr>
<tr><td>Balloon burst testing
n=5 per balloon length/diameter</td><td>95% CI, 99.9% probability, that the catheters do not experience a balloon, shaft or seal integrity failure @ the rated balloon burst pressure (RBP).</td><td>Mean results presented below. For all testing, Standard Deviation (SD) was < 2.0 ATM
<table>
<tr><th>Balloon (dia.)</th><th>Labeled RBI (ATM)</th><th>Burst Pressure (avg.) (ATM)</th></tr>
<tr><td>2.5 dia. 9-20 mm</td><td>16</td><td>24.9</td></tr>
<tr><td>2.75 dia. 9-20 mm</td><td>16</td><td>24.2</td></tr>
<tr><td>2.75 dia. 24-32 mm</td><td>16</td><td>23.0</td></tr>
<tr><td>3.00 dia. 9-32 mm</td><td>16</td><td>25.7</td></tr>
<tr><td>3.00 dia. 32 mm</td><td>16</td><td>25.7</td></tr>
<tr><td>3.5 dia. 9-24 mm</td><td>16</td><td>24.6</td></tr>
<tr><td>3.5 dia. 32 mm</td><td>16</td><td>23.8</td></tr>
<tr><td>4.0 dia. 9-32 mm</td><td>14</td><td>25.2</td></tr>
</table>
PASS</td></tr>
<tr><td>Compliance labeling</td><td colspan="2">
<table>
<tr><th>Pressure (Atm)</th><th colspan="5">Stent Diameter (mm) Nominal Size</th></tr>
<tr><td></td><td>2.5mm</td><td>2.75mm</td><td>3.0mm</td><td>3.5mm</td><td>4.0mm</td></tr>
<tr><td>5</td><td>2.30</td><td>2.64</td><td>2.82</td><td>3.30</td><td>3.75</td></tr>
<tr><td>6</td><td>2.36</td><td>2.70</td><td>2.88</td><td>3.39</td><td>3.83</td></tr>
<tr><td>7</td><td>2.43</td><td>2.77</td><td>2.94</td><td>3.46</td><td>3.92</td></tr>
<tr><td>8</td><td>2.49</td><td>2.82</td><td>3.01</td><td>3.53</td><td>4.01</td></tr>
<tr><td>9</td><td>2.54</td><td>2.87</td><td>3.06</td><td>3.59</td><td>4.08</td></tr>
<tr><td>10</td><td>2.59</td><td>2.92</td><td>3.11</td><td>3.65</td><td>4.15</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td colspan="2"><table>
<tr><td>11</td><td>2.64</td><td>2.97</td><td>3.17</td><td>3.71</td><td>4.21</td></tr>
<tr><td>12</td><td>2.68</td><td>3.00</td><td>3.21</td><td>3.76</td><td>4.27</td></tr>
<tr><td>13</td><td>2.72</td><td>3.04</td><td>3.25</td><td>3.80</td><td>4.32</td></tr>
<tr><td>14</td><td>2.74</td><td>3.07</td><td>3.29</td><td>3.83</td><td>4.36</td></tr>
<tr><td>15</td><td>2.77</td><td>3.10</td><td>3.32</td><td>3.87</td><td>4.40</td></tr>
<tr><td>16</td><td>2.81</td><td>3.13</td><td>3.34</td><td>3.90</td><td>4.43</td></tr>
</table></td></tr>
<tr><td>Balloon Deflatability Testing
n=6</td><td>No significant interference between the stent and balloon</td><td>Min/Max size testing showed no difference between the removal force of the balloon along samples versus the balloon/stent samples.

PASS</td></tr>
<tr><td>Balloon inflation or deflation time
n=40</td><td>Inflation/deflation time, < 20 seconds</td><td>Inflation times ranged from 3.2-7 sec Deflation times ranged from 2.4-7.4 sec.

PASS</td></tr>
<tr><td>Stent securement
n=95</td><td>Securement force > hand-crimped Maxxum PTCA dilatation catheters.</td><td>All samples exceeded the hand-crimped samples.

PASS</td></tr>
<tr><td>Premounted stent deliverability:
o Flexibility
n=3</td><td>Force needed to bend the samples shall be less than that needed to bend other commercially available stents</td><td>All samples met the success criteria</td></tr>
<tr><td>o Crossing profile</td><td><table>
<tr><td>Stent dia.</td><td>Acceptance Criteria</td></tr>
<tr><td>2.5</td><td>≤ 1.05 mm</td></tr>
<tr><td>2.75</td><td>≤ 1.1 mm</td></tr>
<tr><td>3.0</td><td>≤ 1.15 mm</td></tr>
<tr><td>3.5</td><td>≤ 1.2 mm</td></tr>
<tr><td>4.0</td><td>≤ 1.4 mm</td></tr>
</table></td><td>All samples met the success criteria</td></tr>
<tr><td>o Trackability</td><td>Trackability, as measured by the force to track the device, is better than other commercially available stent system values.</td><td>All samples met the success criteria</td></tr>
<tr><td>o Flare Out</td><td>NA, measured and compared the flare-out to NIR samples.</td><td>Similar flare-out

PASS</td></tr>
</table>

Deployment deflatability	Deployment pressure ≤ 8 ATM	All samples met the success criteria PASS
Multiple inflation n=40	Withstand 10 repeated inflations to the RBP of the stent.	All samples met the success criteria PASS
Catheter Withdrawal force	Withdrawal force <510grams (1.1 lbs)	All samples met the success criteria PASS

All test results demonstrated that the NIRflex™ Stent met the product design specifications.

9.4. Packaging and Sterilization Testing

The packaging of the NIRflex™ Premounted Coronary Stent System has the following components:

a) A mandrel in the guide wire lumen at the distal end of the catheter
b) Protective sheath that covers and protects the stent
c) A hooped protective carrier tube to protect the Premounted Stent.
d) An internal sterilization pouch, which is made of Tyvek and plastic film. The pouch is heat-sealed. This pouch holds and protects the protective carrier tube.
e) An external sterilization pouch, which is made of paper and plastic film. The external pouch is heat-sealed. The external pouch holds the internal pouch and forms a second sterilization barrier.
f) A protective carton box, which holds the external pouch and protects the pouch and Premounted Stent against physical damage.

The pouches and the heat-sealing machine were validated to assure compliance to specifications and standard operation procedures.

The NIRflex™ Premounted Coronary Stent System is sterilized using a 90% ethylene oxide (EtO) and 10% CO_2 mixture at 45^0 C. The systems were tested for EtO residual limits specified in the AAMI and ISO guidelines. Pyrogen testing is conducted according to the LAL method. Both tests are conducted routinely on every sterilization lot.

9.5. Shelf Life

The one year shelf life of the NIRflex™ Premounted Coronary Stent System was validated using real time aged, 7 months minimum, samples which were then subjected to

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additional accelerated aging to meet the one year time frame. Under the *"One Year Shelf Life Study for NIRflex™ Premounted Stent"* test protocol system samples were aged for 30.5 days at 45° C, according to a modified Arrhenius equation. Aged samples were then performance tested for: Balloon Burst, Multiple Balloon Inflation, Balloon Inflation/Deflation, Stent Compliance, Catheter Force at Breakage, Guide Wire Compatibility, Guiding Catheter Compatibility, Withdrawal Force, Stent Foreshortening/Uniformity, Stent Securement, and Stent Crimped Profile. These tests and their acceptance criteria are the same as previously identified in the performance testing section (8.3.) Results indicated that all samples passed the acceptance criteria.

10. Summary of Clinical Studies

Following is a list of the Clinical Studies conducted with the NIRflex™ Premounted Coronary Stent System:

- US Clinical Experience
    - NIRflex™ US Study with the NIRflex™ Premounted Coronary Stent System (the subject of this application)
- Non-US Clinical Experience
    - NIRflex™ Pilot Studies using the NIRflex™ Coronary Stent Systems.
    - NIR® TOP Trial using the NIRflex™ Premounted Coronary Stent Systems.

All clinical studies were performed in accordance with the World Medical Association Declaration of Helsinki. Additionally, country specific guidelines, laws and regulation concerning clinical investigations were followed as applicable.

10.1. NIRflex™ US Study

Study: The NIRflex™ Premounted Coronary Stent System was used to treat a total of 205 patients at 11 North American investigational sites in the NIRflex™ US Study. These patients are compared to a total of 848 patients that were treated with the NIR® stent or Palmaz-Schatz (PS®) stent in the NIRVANA Randomized Clinical Trial (RCT).

Purpose: To collect information about the safety and effectiveness of the NIRflex™ Premounted Coronary Stent System in the treatment of *de novo* and restenotic native coronary artery lesions, at 30 days, 6 months and 1 year post index stenting procedure. The primary endpoint was Major Adverse Cardiac Events (MACE) Rate at 30 days post procedure, as compared to the 30-day MACE rate of the pooled NIR stent and PS® stent arms from the NIRVANA Randomized Clinical Trial (NIRVANA RCT).

Conclusions: Multi-center (11 Investigational Sites) clinical data demonstrated the safety and effectiveness at 180 days of the NIRflex™ Premounted Coronary Stent System in the treatment of native *de novo* and restenotic coronary artery lesions (length less than or equal to 25mm).

Design: The NIRflex™ US Study is a non-randomized, prospective, multicenter registry.

Demography: Patients with ischemic coronary artery disease who were candidates for elective stenting procedure of a single stenotic (*de novo* or non-instent restenotic) lesion in a native coronary artery were eligible for inclusion. All lesions were to be ≤ 25mm in length with visual reference vessel diameter of ≥2.5mm and ≤4.0mm.

Methods: The patients underwent balloon angioplasty with an appropriate balloon diameter up to 0.5 mm smaller than the reference vessel diameter. A NIRflex™ Premounted Coronary Stent System of the appropriate size was then selected and deployed in the native coronary artery. If stent sizing/apposition required optimization, the Premounted Stent balloon, or another balloon catheter of the appropriate size, was to be re-deployed to the stented area using standard angioplasty techniques. Inflations were to be repeated until the desired result was achieved. All patients received the hospital's standard anticoagulant and anti-platelet regimen for coronary stent implantation. Patients were clinically followed for 30 days and 6 months. An independent Clinical Events Committee (CEC) adjudicated all major clinical endpoints for the Study.

Results: Table 3 shows the principal effectiveness and safety results for the NIRflex™ US patients compared with the NIRVANA RCT patients.

Gender Bias: Of the 205 patients enrolled, 140 (68.3%) were male. The ratio of males to females in this study is consistent with other trials of coronary stents.

Univariate logistic regression analyses were conducted to evaluate the effect of gender on the following clinical outcomes: 30-day MACE, 180-day MACE, technical success, and procedural success. One-way analysis of variance was used to assess effect of gender on the angiographic outcomes final in-stent minimal lumen diameter (MLD) and final in-stent percent diameter stenosis.

Gender was not significantly associated with any of the clinical outcomes ($p>0.30$). It was not associated with final in-stent MLD ($p=0.98$) and was only marginally associated with final in-stent diameter stensosis ($p=0.09$). The average difference (calculated as males minus females) in percent diameter stenosis was 2.65% (95% confidence interval of -0.47% to 5.77%). Since outcomes were not associated with gender, these data demonstrated that gender was not an influencing factor on safety or effectiveness.

Table 3. Principal Effectiveness and Safety Results
All patients in NIRflex™ US Study and NIRVANA RCT
%, [95% Confidence Interval], (Number)

Efficacy Measures	NIRFLEX™ US (N=205 Patients, N=207 Lesions)	NIRVANA (N=848 Patients, N=851 Lesions)	Difference [95% C.I.]*	Pvalue
Technical Success	96.5% (194 / 201)	98.7% (819 / 830)	-2.2% [-4.0%,0.0%]	0.10
Procedural Success	94.0% (189 / 201)	94.8% (787 / 830)	-0.8% [-5.2%, 2.3%]	0.62
Post-Procedure In-Stent Minimal Lumen Diameter (MLD, in mm)				
Mean±SD (N)	2.72±0.47 (203)	2.79±0.43 (833)		
Range (min,max)	(1.50,3.92)	(0.00,4.30)	-0.06 [-0.13,0.01]	0.59
Post-Procedure In-Stent Percent Diameter Stenosis (% DS)				
Mean±SD (N)	4.22%±10.72% (203)	8.26%±11.68% (833)		
Range (min,max)	(-40.94%,37.42%)	(-38.81%,100.00%)	-4.0% [-5.8%,-2.3%]	0.09
TLR-Free at 30 days	99.5%	99.1%	0.4% [-0.9%,1.7%]	0.92
TLR-Free at 180 days	93.4%	92.6%	0.8% [-3.2%,4.8%]	0.38
TVR-Free at 30 days	99.0%	98.6%	0.4% [-1.4%,2.2%]	0.91
TVR-Free at 180 days	92.4%	91.2%	1.2% [-3.1%,5.5%]	0.37
TVF-Free at 30 days	96.4%	95.3%	1.1% [-2.1%,4.4%]	0.40
TVF-Free at 180 days	88.3%	87.5%	0.8% [-4.4%,5.9%]	0.43
MACE-Free at 30 days	96.9%	95.6%	1.3% [-1.8%,4.3%]	0.25
MACE-Free at 180 days	89.3%	88.8%	0.5% [-4.4%,5.5%]	0.44

Safety Measures and Other Clinical Events (to 180 days)	NIRFLEX™ US (N=205 Patients, N=207 Lesions)	NIRVANA (N=848 Patients, N=851 Lesions)	Difference [95% C.I.]	Pvalue
In-Hospital MACE	2.9% (6 / 205)	4.1% (35 / 848)	-1.2% [-3.4%, 2.5%]	0.70
Out-of-Hospital MACE	7.3% (15 / 205)	7.0% (59 / 848)	0.4% [-3.1%, 5.0%]	0.55
Cumulative Incidence of MACE	10.2% (21 / 205)	11.1% (94 / 848)	-0.8% [-5.0%, 4.6%]	0.35
Stent Thrombosis	0.5% (1 / 205)	0.5% (4 / 848)	0.0% [-2.3%, 2.4%]	-
Perforation	0.0% (0 / 205)	0.5% (4 / 848)	-0.5% [-2.5%, 1.6%]	-
Bleeding Complications	1.5% (3 / 205)	1.2% (10 / 848)	0.3% [-1.1%, 3.2%]	0.33
Vascular Complications	3.4% (7 / 205)	4.5% (38 / 848)	-1.1% [-4.9%, 2.6%]	0.57
CVA	0.0% (0 / 205)	0.4% (3 / 848)	-0.4% [-2.3%, 1.7%]	-

* Technical Success, Procedural Success and Safety Measures confidence intervals for proportions calculated using the method of Newcombe (*Statistics in Medicine*, 1998). Remaining confidence intervals for proportions calculated using approximation to normal distribution.

Definitions:

Technical Success: Successful delivery and deployment of the NIRflex™ stent to the intended site without use of a device outside the treatment strategy, and achievement of less than 50% final residual diameter stenosis.

Procedural Success: Technical success without in-hospital MACE.

QCA: Quantitative Coronary Angiography

% DS: Diameter Stenosis

The following survival estimates are by Kaplan-Meier methods:

TLR-Free: No target lesion revascularization.

TVR-Free: No target vessel revascularization.
TVF-Free: No death, myocardial infarction, or target vessel revascularization.
MACE-Free: No death, myocardial infarction, or target lesion revascularization.
Major Adverse Cardiac Events (MACE): Death, myocardial infarction, and target lesion revascularization.

NIRflex™ OUS Clinical Experience

10.1.1. NIRflex™ Pilot Studies

Two separate, non-randomized, single-center studies were conducted in Israel and Italy. A total of 45 patients were enrolled and followed clinically for 30 days and 6 months. These clinical evaluations aimed to provide safety and feasibility data regarding the use of the NIRflex™ and another stent marketed outside of the U.S. in the treatment of stenotic lesions in native coronary arteries. An independent Clinical Events Committee (CEC) adjudicated all major clinical endpoints for the Studies. Within the NIRflex™ Italy Pilot Study, 6 additional patients were treated using the NIRflex™ Premounted Coronary Stent System (the subject of this application). Six-month safety and performance data from the NIRflex™ Pilot Studies showed that the premounted stents performed as expected.

The acute clinical results for patients treated in Italy showed that the technical success rate, defined as successful delivery and deployment of the NIRflex™ or the other stent to the intended site and achievement of less than 50% final residual diameter stenosis, as assessed by QCA, was 90% (27/30). The procedural success rate defined as technical success without in-hospital major adverse cardiac events (MACE) was 88% (21/24). The cumulative incidence of MACE was 0.0% (0/24) at 30 days and 0.0% (0/24) at 180 days.

The acute clinical results for patients treated in Israel show the technical success rate was 100% (21/21). The procedural success rate was 100% (15/15). The cumulative incidence of MACE was 0.0% (0/15) at 30 days and 20% (3/15) at 180 days.

10.1.2. NIR® TOP Trial

NIR® TOP Trial was a randomized clinical trial with the NIRflex™ Premounted Coronary Stent System (the subject of this application) and another stent system marketed outside of the U.S. conducted in Canada, Europe and Israel. A total of 305 patients were enrolled from January 2002 to June 2002. All patients were followed clinically and angiographically to 6 months.

The NIRflex™ Premounted Stent arm of the NIR® TOP study demonstrated excellent procedural outcome (procedural success of 96.8%), excellent early and late clinical outcomes (2.5% in-hospital MACE and 7% TLR at 210 days), and favorable angiographic results (late loss of 0.65 and angiographic restenosis rate of 17.8% in coronaries with average reference vessel diameter of 2.74mm), all of which are

comparable to those of other commercially available coronary stents and those of the NIRflex® US trial results.

11. Conclusions Drawn from Studies

11.1. Safety and Effectiveness

Multi-center (11 Investigational Sites) clinical data demonstrated the safety and effectiveness at 180 days of the NIRflex™ Premounted Coronary Stent System in the treatment of native *de novo* and restenotic coronary artery lesions (length less than or equal to 25mm).

The *in vivo* non-clinical and laboratory studies together with the clinical investigation provide valid scientific evidence and provide reasonable assurance that the NIRflex™ Premounted Coronary Stent System is safe and effective for its intended use.

12. Panel Recommendation

Pursuant to section 515(c)(2) of the Federal Food Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory Panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by the panel.

13. FDA Decision

CDRH issued a letter to Medinol, Ltd. on May 21, 2003 advising that the PMA was approvable subject to acceptable results from inspection of the manufacturing facilities. The applicant's manufacturing facility was inspected on August 17, 2003 and was found to be in compliance with the Quality System Regulation (21 CFR 820). CDRH approved this PMA on October 24, 2003.